REMARKS / ARGUMENTS

As noted on the Request for Continued Examination transmittal letter, Applicants request that the Examiner ***not*** consider the 37 CFR § 1.116 Amendment filed on June 10, 2004.

Upon entry of this amendment, the claims pending are claims 1-11, 13-17, 28-37, and 39-43. Claims 18-23 and 27 were cancelled by previous amendments. Paragraphs (a) (ii) and (b) (ii) of Claims 1 and 43 have been cancelled by amendment. The newly cancelled subject matter from Claims 1 and 43 stands canceled without prejudice to refiling as non-elected subject matter, as does the subject matter of Claims 18-23. Further, Claims 12, 24-26, and 38 are canceled, without prejudice, in an effort to place the application in condition for allowance.

Claims 2, 4-9, 11, 28, 30-35, and 37 are amended to clarify the invention in view of the above restriction of the subject matter of Claims 1 and 43. Claims 16 and 42 are amended to correct minor clerical errors. No new matter was added by these amendments, which are supported in the original specification and by the original claims.

Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation application filed during the pendency of this application. Applicants further affirm the correctness of the inventive entity in view of the cancellation of the non-elected claims.

The specification was amended to insert the sequence listing of wild-type cholera holotoxin subunit A as described below and refer to the same on page 38. The same sequence appears in Mekalanos *et al*, **1983** *Nature*, 306:551-557 in the context of the entire cholera toxin sequence with subunit B and 5' and 3' untranslated regions. The mature subunit A is indicated by the first amino acid appearing under the first mature amino acid "N" in the sequence. SEQ ID NO: 1 is a duplicate of the mature subunit A sequence as set forth in International Patent Publication No. WO 93/13202 (Domenighini), incorporated by reference in the specification at page 38, lines 27-28. Because the sequence of wild-type subunit A was properly incorporated by reference by reference to Domenighini in the specification, no new matter is added by these amendments.

Claim Rejections based on 35 USC §112, first paragraph

> Claims 12 and 38 are rejected as allegedly failing to comply with the enablement requirement and containing subject matter not described in the specification in such a way as to show possession of the claimed invention. Specifically, the examiner states that the plasmid DNA encoding HSV gD2 antigen has not been described. The examiner requires the applicant to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant stating that the amendatory material consists of the same material incorporated by reference in the referencing application.

The cancellation of Claims 12 and 38 moots the outstanding rejection. As noted above, these claims were canceled, without prejudice, in an effort to place the application in condition for allowance. Applicants reserve the right to prosecute these claims in a continuation application filed during the pendency of the present application.

Withdrawal of this rejection is requested.

Claim Rejections based on 35 USC §112, second paragraph

> Claims 1-17 and 24-43 are rejected under 35 USC §112, second paragraph, for alleged indefiniteness in view of lack of a reference sequence for the position numbers in the claims.
>
> The examiner asserts that the cholera toxin subunit A is known to have sequence variation, referred to Swiss Prot Accession Nos. Q8vL16, Q81356, and P01555, and thus a reference sequence is necessary.
>
> The examiner states that Applicant is required to amend the disclosure to include the material incorporated by reference, including a declaration as stated previously.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims, specification, and the following remarks.

The cancellation of Claims 12, 24-27 and 38 moots the outstanding rejection as applied to these claims.

As stated in detail below, the sequence of CT-A, both wild-type (WT) and variants, are known in the art. All variants of CT-A contain a glutamic acid at

position 29. Further, position 29 is clearly identified in the specification by reference to its native glutamic acid residue. One cannot locate a position 29 having a glutamic acid unless one counts from the native protein amino acid 1, not from the well-known 18 amino acid signal sequence of CT-A

Regarding the identity of the amino acid position numbers, Applicants draw the examiner's attention to the documents cited in the specification, i.e., Mekalanos *et al*, **1983** *Nature*, 306:551-557, (as "Bibliography entry 1" on page 2, lines 3-4 and as the first citation on page 114, labeled "Bibliography") and Domenighini et al., International Patent Publication No. WO 93/13202 (page 38, lines 10 and 27). Mekalanos is the standard reference in the art for the well-known sequence of cholera toxin and its subunits. Further, Domenighini also provides the amino acid sequence of the same mature CT-A subunit cholera toxin and its subunits. Such sequences are also available in the NCBI database, as submitted by the authors of the above-noted publication.

Thus, in publications throughout the art, a reference to position 29 of wild-type cholera toxin subunit A is understood by those of skill in the art to mean the highlighted amino acid in the well-known sequence of subunit A. Note that in a variety of publications, the authors use the same convention for identifying amino acid positions of cholera toxin subunit A, i.e., by identifying the amino acid by position number with a reference to Mekalanos. Such publications did not feel it necessary to set out the well-known sequence. See, e.g., International Patent Publication Nos. WO 97/02348 and WO 97/29771 and background references cited therein; and Vadheim K.L, *et al*, **1994** *Microb. Pathog., 17*(5):339-46.

The specification of the present application clearly states on page 4, lines 4-6 that the present invention is performed using "... a mutant cholera holotoxin featuring a point mutation at amino acid 29 of the A subunit, wherein the glutamic acid residue is replaced by an amino acid other than aspartic acid". ***Applicants' only requirement*** is that the ***amino acid at position 29*** of the sequence of cholera holotoxin A subunit be ***a glutamic acid***.

While Applicants agree with the Examiner that cholera toxin subunit A is known to have sequence variations (e.g., Swiss Prot Accession No. P01555, Q8VLI6,

and Q8L356), the sequences of all of these cholera holotoxin subunit A variants ***contain a glutamic acid at position 29***. Therefore, Applicants' claims properly encompass the substitution of any CT-A with a glutamic acid at position 29.

> Applicants respectfully disagree with the Examiner's statement that:
>
> "[i]t is not clear whether the A-subunit could be in the pro-toxin form or in the form where the signal sequence has been cleaved" and that "...the numbering from the N-terminal of the protein antigen would result in a different position for substitution of the amino acid" at position 29.

One of skill in the art would readily understand, based upon the teachings of Mekalanos in 1983 (see the mature CT-A sequence in Domenighini), that the sequence of cholera holotoxin contains an N-terminal 18 amino acid signal sequence and that the mature protein begins at the asparagine amino acid position 19 (see page 552, paragraph 1, lines 6-7). Further, based on the teachings of the instant specification that position 29 of the amino acid sequence of cholera holotoxin must be a glutamic acid, the sequence thereby cannot possibly include the N-terminal 18 amino acid signal sequence.

In an effort to place the application in condition for allowance and as suggested by the Examiner, Applicants have amended the specification by inserting the amino acid sequence of the wild-type cholera holotoxin subunit A as recited in Mekalanos and Domenighini, amended certain paragraphs in the specification on page 38 to refer to the sequence of the same as SEQ ID NO: 1, and enclosed a Declaration executed by the below-noted attorney of record asserting that the amendatory information being inserted was properly incorporated by reference.

In view of these amendments and remarks, Applicants submit that all claims are now in condition for allowance and that this rejection may be properly withdrawn.

Claim Objections

> Claims 12 and 38 are objected to because they depend from sections of the independent claim which have been withdrawn from consideration. Amendment in independent form would obviate this rejection.

The cancellation of Claims 12 and 38 moots the outstanding rejection. As noted above, these claims were canceled, without prejudice, in an effort to place the

application in condition for allowance. Applicants reserve the right to prosecute these claims in a continuation application filed during the pendency of the present application.

Withdrawal of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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